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Use of anticonvulsants drugs for neuropathic painful conditions

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Abstract

Neuropathic pain, a form of chronic pain initiated and sustained by an insult to the peripheral or central nervous system, is a challenge to clinicians as it does not respond well to traditional pain therapies. However exact pathophysiology is not known but considering similarities between epilepsy models and in neuropathic pain models justify the rationale for use of anticonvulsant drugs in the symptomatic management of neuropathic pain disorders. The role of anticonvulsant drugs in the treatment of neuropathic pain is evolving and various clinical trials have used these anticonvulsants and shown positive results in the treatment of trigeminal neuralgia, painful diabetic neuropathy and postherpetic neuralgia. The availability of newer anticonvulsants tested in higher quality clinical trials has marked a new era in the treatment of neuropathic pain. Gabapentin has the most clearly demonstrated analgesic effect for the treatment of neuropathic pain, specifically for treatment of painful diabetic neuropathy and postherpetic neuralgia. Pregablin is a newer drug and will soon gain popularity in clinical practice. There is a need for further advances in our understanding of the neuropathic pain syndromes to establish the role of anticonvulsants in the treatment of neuropathic pain.

Introduction

Neuropathic pain is defined as pain initiated and sustained by an insult to the peripheral or central nervous system or both. It responds poorly to traditional therapeutic approaches and to 'standard' doses of conventional analgesics. In this article we would review the clinical

evidences regarding the clinical use of anticonvulsants in current practice for common painful neurological conditions like trigeminal neuralgia, postherpetic neuralgia and diabetic neuropathy.

Postherpetic neuralgia (PHN) is defined as pain that persists 1 to 3 months following the rash of herpes zoster (HZ). The pain of PHN is generally described as burning and continuous in nature. There may be both lancinating pain and dysethesias. Typically the pain characteristically spreads along a single dermatome from the central dorsal line in a ventral direction, concordant with the dermatomal rash.

Trigeminal neuralgia (TGN) is caused by trigeminal nerve compression by vessels (especially arteries, but occasionally veins) or tumours. As a result of this pressure, myelin is lost and leads to abnormal depolarization and reverberation, resulting in ectopic impulses manifested as pain. The pain has been described as "electric shock-like" or "stabbing". The pain usually lasts from one to several seconds, but may occur repetitively. A refractory period of several minutes during which a paroxysm cannot be provoked is common.

Painful diabetic neuropathy (PDN) is caused by the involvement of small nerve fibres, which may affect without objective clinical findings. Smaller fibre neuropathy may manifest as a number of different clinical symptoms, including allodynia, burning pain, defective warm thermal sensation and defective autonomic function.

The aim of this review is to discuss the current trends of anticonvulsant use in common neuropathic painful conditions listed above.

Method - Search Strategy

In this review, we attempt to cover common painful neuropathic conditions in Pakistani population. Using pre defined search terms related to anticonvulsants and neuropathic pain (anticonvulsants for neuropathic pain, gabapentin, phenytoin, lamotrigine, pregabalin, carbamazepine, sodium valproate, trigeminal neuralgia, diabetic neuropathy and post herpetic neuralgia) this review was searched from Pub Med 1992-2007, Yahoo and Google web site.

History of Anticonvulsants in Clinical Practice

Similarities between epilepsy and neuropathic pain have been observed for over 100 years. The first report of analgesia with an anticonvulsant in neuropathic pain was with phenytoin in 1942. In 1962, carbamazepine came into use and has subsequently remained the most widely used anticonvulsant drugs to combat neuropathic pain,¹ until the recent introduction of gabapentin (a structural analogue of the inhibitory neurotransmitter gamma amino butyric acid (GABA)). The gabapentin is currently very popular among pain physicians for chronic neuropathic painful conditions. Lamotrigine is a novel agent that is chemically different from other antiepileptic drugs. Several types of neuropathic pain have been successfully treated with lamotrigine in randomized control trials as well as in anecdotal reports. Pregabalin is a GABA analogue with similar structure and actions to gabapentin. It has antiepileptic, analgesic and anxiolytic activity. Pregabalin is a safe and well-tolerated new treatment for neuropathic pain.

Mechanism of Neuropathic Pain

Many pathophysiological processes have been observed in neuropathic pain models but exact mechanism of neuropathic pain is unknown.

Various hypotheses about the pathophysiological process that have been described range from the cellular to the intranuclear level. At the cellular level, there is the formation of microneuromas and spontaneous ectopic generators, development of ephaptic transmission, and sensitivity to circulating catecholamines. In the neuronal cell membrane, there is the alteration of Na⁺ channels, Ca²⁺ channels and neurotransmitter systems including substance P, NMDA, γ aminobutyric acid (GABA) and opioid systems. At the intracellular level, there is the activation of a number of second messenger cascades [with adenosine, protein kinase (PK) A and PKC being those best documented], and on the nuclear level, there is the activation of immediate early genes.

Assessment of Neuropathic Pain

Advances in the diagnosis and treatment of neuropathic pain have been hampered by the absence of consensus on its diagnostic criteria, the lack of scales to assess the intensity of the neuropathic pain symptoms, to determine the efficacy of treatments and to differentiate patients with neuropathic pain from nonneuropathic pain.

The Neuropathic Pain Scale (NPS) and Neuropathic Pain Symptom Inventory (NPSI) have been designed. As these scales do not differentiate patients with neuropathic pain from patients with nonneuropathic pain, three questionnaires were designed to do this: the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS), the Neuropathic Pain Questionnaire (NPQ), and the neuropathic pain diagnostic questionnaire called the DN4. Studies to compare the accuracies sensitivities and specification of various questionnaires are lacking in identifying patients with neuropathic pain.²

Use of Anticonvulsants in Painful Conditions

Besides epilepsy anticonvulsant drugs are extensively used in several psychiatric and neurological disorders including migraine, neuropathic pain, bipolar disorder, mania, schizophrenia, anxiety, and tremor. These disorders are related to disturbed excitability in the CNS and they may possibly share pathophysiological processes. The main neurobiological mechanisms responsible for the clinical efficacy of anticonvulsant drugs in these disorders include disturbance in GABAergic or glutamatergic neurotransmission or alteration of voltage-gated ion channels or intracellular signaling pathways.

The main targets for anticonvulsant drugs in the synapses include enhancement of GABAergic inhibitory neurotransmission, decrease in glutamatergic excitatory neurotransmission directly or via inhibition of voltage-dependent sodium and calcium channels, and interference with intracellular signaling pathways.^{3,4}

Recent Trends of Anticonvulsants Algorithm

It is very difficult to formulate an algorithm because of lack of comparative studies between existing and new drugs. If only one set of criteria: pain relief is used then the list of drugs for neuropathic pain look like this: TCA > opioids = tramadol = gabapentin/pregabalin. If the criteria for efficacy are based on both pain relief and quality of life measures then such data are not existent for several of the old compounds such as TCA, carbamazepine, and phenytoin and the list is likely to look as follows: gabapentin/pregabalin > tramadol > opioids > TCA.⁵

Limitations with Antiepileptic Drug Use

Various side effects have been reported with the use of anticonvulsant drugs varying from dizziness, diplopia to life threatening rashes, blood dyscrasias and hepatotoxicity.

Current Recommendations in Different Common Pain Syndromes

Carbamazepine (CBZ)

Carbamazepine slows recovery rate of voltage-gated Na⁺ channels, Minor Ca²⁺ channel antagonist effect and is chemically related to tricyclic antidepressants

Use of CBZ has been most frequently documented in TGN and PDN. Use of CBZ in patients with TGN was first reported in 1962.¹ CBZ has been compared to placebo in 6 different studies in a randomized double blind clinical trials.⁶⁻¹¹ All these trials proved the efficacy of CBZ with a response rate of 56 to 75% with 0 to 26 % with placebo. CBZ was found to be superior to placebo with statistically significant difference. However there were many limitations. All the trials were small and short term and used simple measures for pain outcome. In addition, diagnostic criteria were not clearly stated and previous treatment and duration of pain varied considerably.

Various side effects have also been observed in different studies and 50% of CBZ group patients have presented side effects such as drowsiness, dizziness, ataxia, nausea and vomiting. There were 1-2 dropouts in the study due to skin erythema.^{6,10,11} One patient had low platelet count.¹¹

We found only one retrospective cohort study of 143 patients with TGN in which long term effect (over 16-years) of CBZ was evaluated.¹² The drug was effective initially with few mild side effects in 99 patients (69%). Of these, 19 developed resistance later, i.e. between 2 months and 10 years after commencing treatment, and required alternative measures. Of the remaining 80 (56%), the drug was effective in 49 for 1- 4 years and in 31 for 5-16 years. Twenty five percent patients failed to respond to CBZ and 6% were intolerant to CBZ due to rash, nausea and thirst and water intoxication in 6, 1 and 1 patient respectively which necessitated cessation of the drug. This study has thus confirmed the efficacy of CBZ for the treatment of TGN and proved that it may continue to be effective for many years.

CBZ was the first anticonvulsant studied for the treatment of PDN. Three randomized trials evaluating CBZ in PDN used double-blind, crossover techniques. Two small, placebo controlled, double-blind, crossover trials found CBZ to be superior to placebo and effectively reduce pain. In one study¹³ 600 mg/day was used and 28 out of 30

patients reported pain relief. Two patients withdrew from the study because of rash. In another study¹⁴ with 40 patients, those treated with CBZ 200mg in three divided doses had statistically significantly less pain on day 10 and 14 than those who received placebo. A third study used an active control group with combination of nortriptyline and fluphenazine (tricyclic neuroleptic).¹⁵ Sixteen patients were recruited in this study. Both therapies produced significant improvement of pain and paraesthesia but there was no statistically significant difference in pain relief in favour of carbamazepine. Although adverse effects were mild and more frequent when patients were being treated with tricyclic neuroleptic combination, no statistical analysis was performed to detect the difference between the two groups.

We could not find any study which could give favourable clinical evidence of use of CBZ in PHN.

In summary, efficacy of carbamazepine in neuropathic pain has been demonstrated in early studies, and this has since been confirmed in randomized controlled trials. In TGN comparison of all of the studies in which carbamazepine was compared with placebo showed pain relief, lower pain ratings or both. Efficacy is also seen in relieving pain in patients with PDN in 3 out of 3 studies. Carbamazepine did not gain popularity because of its adverse effects which ranged from somnolence, dizziness and gait disturbance. In earlier studies, haematopoietic issues were addressed but no patients were excluded because of them. Dizziness and somnolence were the most frequent tolerable adverse effects.

Phenytoin

Analgesic effect of phenytoin is achieved through the blockage of Na⁺ channels, inhibition of presynaptic glutamate release and suppression of spontaneous neuronal ectopic discharges.

Phenytoin was the first anticonvulsant to be used successfully to treat patients with neuropathic pain in TGN. We came across 2 double-blind, placebo-controlled, crossover trials of phenytoin on PDN which showed opposite results. In a trial of 12 patients, phenytoin failed to show any benefit over placebo.¹⁶ The second trial¹⁷ which included 38 patients, showed a statistically significant difference in favour of phenytoin. This variability in results could be due to the differences in study design, including sample size and length of follow-up.

In summary patients often require large doses, increasing the risk of side effects. Common adverse effects include dizziness, unsteadiness and drowsiness. Adverse effects in both the studies on PDN were around 10%. However, it is usually poorly tolerated, so is therefore less preferred.

Valproic Acid

Valproic Acid slows recovery rate of voltage-gated Na⁺ channels, limits repetitive firing. Moreover, valproic acid increases the amount of GABA in the brain, enhancing the activity of glutamic acid decarboxylase and inhibiting GABA degradation enzymes.

Valproate has a 65% efficacy rate in the treatment of TGN, but it can take several weeks before patients respond. There are no reports on the isolated use of valproic acid and it is difficult to assess its relative contributions.

At present, the precise role of valproic acid in the treatment of neuropathic pain has not been determined and additional randomised trials are still necessary to document the possible effect of valproic acid for neuropathic pain due to peripheral disorders such as PDN.

Gabapentin

Gabapentin is one of the new generation of antiepileptic drugs used for treatment of neuropathic pain. It is found to be perhaps the best agent studied so far. It was developed as a structural GABA analogue but it has no direct effect on GABA receptors and it does not affect GABA uptake or metabolism but a magnetic resonance imaging spectroscopy study documented a global increase in GABA after the administration of gabapentin. There are various evidences that it binds to alpha-2-delta subunit of voltage-gated Ca²⁺ channel (and decrease Ca²⁺ influx into nerve terminal) and inhibits branched chain AA transferase.¹⁸

There is no randomized controlled trial examining the effect of gabapentin in TGN. In all the case series the number of cases reported were small therefore we could not predict its efficacy. None of the case reports had shown any adverse effect. Based on the observations of case series gabapentin can be used as a first line therapy in place of carbamazepine because of few adverse effects, faster titration, no adverse drug intolerance and no known idiosyncratic skin reaction. But there are no recommendations in the literature for its use as a first line therapy.

Various randomised clinical trials have established the efficacy of gabapentin for relief of neuropathic pain in PDN and PHN.

In a large placebo controlled parallel designed randomized clinical trial of 165 patients with 1-5 year history of PDN, gabapentin was initiated at a dosage of 300 mg 3 times daily. 80% were able to escalate the dosage over 2 weeks, from 900 to 3600 mg/day in 3 divided doses. Pain relief was observed during the second week after the dosage reached 1800 mg/day. Pain relief was maintained after a further dose increase and for the

duration of the 8-week study. There was improvement of sleep, mood and quality of life beginning at week one and was controlled throughout the study period. Gabapentin was well tolerated in the study with 70 (83%) of 84 patients completing treatment. Dizziness and somnolence were reported by significantly more patients receiving gabapentin than placebo.¹⁹

One placebo controlled, double blind, and crossover trial of 40 patients of PDN has failed to show any significant difference between gabapentin and placebo. A possible explanation for this lies in the use of a relatively low dosage of gabapentin (900 mg/day) to minimize adverse effects.²⁰ A crossover study with 25 patients compared gabapentin with amitriptyline for treatment of PDN.²¹ In that study, gabapentin was well tolerated and effective but offered no advantage over amitriptyline. The results of these studies suggested that gabapentin is probably ineffective or minimally effective in low doses. Common adverse events for both treatments were sedation, dry mouth, dizziness, postural hypotension, weight gain, ataxia, and lethargy. With the exception of weight gain with amitriptyline, the incidence of these adverse effects did not differ significantly between the groups.

Another study found that the combination of gabapentin and morphine was more effective than either treatment alone for treatment of neuropathic pain and allowed lower doses of each to be used.²² In all these studies gabapentin was found to be effective in the treatment of PDN with tolerable side effects. Only disadvantage appears that the patient requires titrating dosing and multiple daily doses for patients requiring more than 300 mg/day.

Two large clinical trials having essentially a similar design: multicentral randomized, double-blind, placebo-controlled parallel group, of 8 weeks duration, examined the efficacy of gabapentin in PHN.^{23,24} The first 4 weeks were a titration phase during which patients were titrated to tolerability upto a maximum dose and found gabapentin to be effective as a symptomatic treatment of PHN. In one study²³ of 229 patients, the target dose was 3,600 mg/day; a minimum of 1,200 mg/day was acceptable. 65% achieved the target dose, while 83% received at least 2,400 mg/d. Treatment resulted in a statistically significant reduction in the average daily pain score compared with placebo, while improving sleep, mood and quality of life. The side effects of gabapentin include somnolence, dizziness, and (less commonly) mild peripheral oedema; which required dose adjustment but not treatment discontinuation.

The other trial²⁴ of 334 patients compared the efficacy of two fixed doses of gabapentin, 1,800 mg/day and 2,400 mg/day. Unlike the previous study, patients unable to attain the target doses were counted as withdrawals. At the

end of the study, the reduction in pain scores was significantly in favour of both gabapentin treatment groups compared to placebo. Both doses showed efficacy with no significant difference between the two.

In summary, various clinical trials have shown gabapentin to be effective in relieving pain and associated symptoms in patients with PDN and PHN. The dosages used in these studies ranged from 900 to 3600 mg/day given in 3 divided doses. Gabapentin was well tolerated with no significant difference in adverse events with gabapentin compared with placebo. Dizziness and somnolence were the most frequent tolerable adverse effects. Additional clinical trials are necessary to evaluate the efficacy of gabapentin in TGN.

Lamotrigine

Lamotrigine blocks voltage dependent Na⁺ channels with the inhibition of glutamate release.

There is insufficient evidence about the effects of lamotrigine in people with TGN. One small double blind crossover randomized controlled trial compared lamotrigine with placebo, in which 14 people with refractory TGN (using either CBZ or phenytoin) were studied.²⁵ It found more people improved after 2 weeks of treatment with adding lamotrigine to current medication compared with adding placebo. It was a short period study and concurrent use of other medication limits the interpretation. Adverse effects of lamotrigine included dizziness, constipation, nausea and drowsiness. It may also cause serious skin rash and allergic reactions. The total number of people reporting adverse effects was the same as with placebo. There was no drop out with adverse effects. Lunardi et al²⁶ reported lamotrigine to provide impressive and sustained relief of TGN in one small, open-label, prospective study. This was maintained during a follow-up period of 3-8 months. The dosage required for adequate relief varied widely from 100-400 mg/day.

In the first published study of lamotrigine for the treatment of PDN,²⁷ 15 patients were recruited, who received lamotrigine titrated from 25-400 mg/day over 6 weeks. Thirteen patients completed the study and reported significant decrease in pain scores at the end of the study. Two weeks after the end of the study pain was still significantly reduced suggesting lasting effect of lamotrigine. Of the 2 patients who discontinued the study one developed dizziness and ataxia (while taking 400 mg/day) and the other developed rash after the first dose. Symptoms resolved in both patients within 1 week after discontinuation of lamotrigine. In another randomized, placebo-controlled trial²⁸ which enrolled 59 patients with PDN lamotrigine appeared to be effective at a dosage of 200 to 400 mg/day. Significant pain reduction began at week 6 when patients were taking 200 mg/day lamotrigine. The

most common adverse events in both groups were nausea, epigastric pain, headache, drowsiness, and dizziness. None occurred in more than 4 patients in either group. Two patients in each group withdrew due to adverse events. They developed a rash while being treated with lamotrigine, one at a dose of 50-mg/day and the other at a 300 mg/day. In both patients, the rash resolved when lamotrigine therapy was discontinued.

In summary, effectiveness of Lamotrigine in painful conditions is not well described in clinical trials. In all the studies the number of patients was small. Efficacy of lamotrigine in relieving pain in patients with TGN refractory to other treatments, such as carbamazepine, phenytoin or both, which were continued for the duration of the study. Patients experienced tolerable adverse effects: dizziness, constipation, nausea, somnolence and diplopia. More well-designed trials are needed to better define the role of lamotrigine as an analgesic drug in painful neuropathic conditions.

Topiramate

Topiramate blocks voltage-gated Na⁺ channels, affects activity at kainate and AMPA subtype of the glutamate receptor and GABA activity by interacting with a nonbenzodiazepine site on GABAA receptors.

We found one very small double blind cross over randomized controlled trial using topiramate in patients with PHN. In this study patients receiving topiramate had shown 31% to 64 % pain decrease in the primary study, however without statistically significant difference. All patients have referred adverse effects with topiramate including nausea, diarrhoea, irritability, fatigue sedation and decreased cognitive function, however without dropouts.

There were two parallel, placebo-controlled studies, to see the efficacy of topiramate in the treatment of PDN. One showed efficacy after 8 weeks,²⁹ whereas the other, a much larger study, showed no difference between topiramate and placebo.³⁰ Topiramate has many adverse effects, such as cognitive slowing, dizziness, and a small risk of kidney stones and closed-angle glaucoma, and it often is not tolerated by patients. In the larger of the studies, 24% of patients discontinued topiramate because of side effects.³⁰ Topiramate requires careful titration during initiation and withdrawal.

In summary clinical experience with topiramate is limited in neuropathic pain conditions and more large randomized clinical trials are required to establish its efficacy.

Pregabalin

Pregabalin like gabapentin is a GABA analog

without proven agonistic effect on GABA receptors. Pregabalin does not appear to interact directly with Na⁺ channels, Ca²⁺ channels or neurotransmitter responses (GABA, glutamate).

Pregabalin has been evaluated in three parallel, placebo-controlled studies in the treatment of PDN at 75, 150, 300 and 600 mg/day.³¹⁻³³ Both the 75 mg/day and 150 mg / day dosages were found not to differ significantly from placebo but 300 mg/day and 600 mg/day dosages showed good efficacy on pain and function measures. The most common adverse effect associated with 300 to 600 mg/day of pregabalin was dizziness. Pregabalin was relatively well tolerated and causes less sedation than gabapentin.

Use of Pregabalin in PHN was found in two multicentral large parallel group double blind placebo-controlled trials in which the analgesic efficacy of pregabalin was investigated^{34,35} and both trials revealed a superiority over placebo. In one trial,³⁴ a pregabalin dose of either 300 or 600 mg/day, depending on creatinine clearance, was administered as an attempt to obtain a predicted pregabalin plasma concentration in all patients. In another trial³⁵ 238 patients were randomized to receive 150, 300 mg/day pregabalin or placebo for 8 weeks. Pregabalin was effective in relieving pain in patients receiving 150 or 300 mg/day as compared to placebo. These studies have shown significant reduction of pain, on average, within 3 days of initiating pregabalin treatment and there was a reduction in sleep interference at doses of 150 to 600 mg daily. Common side effects were dizziness, somnolence, dry mouth, peripheral oedema and weight gain.

In summary there are limited trials of pregabalin in painful neuropathic conditions but the available clinical trials and clinical experience consistently show improvement in pain and sleep. And it seems that pregabalin will supersede many other anticonvulsants in the treatment of neuropathic pain. Dizziness, somnolence and peripheral oedema were the most frequent adverse effects reported but the withdrawal rate was lower than that seen for other anticonvulsants.

Conclusion

From the available clinical trials and case reports it seems that anticonvulsants are increasingly important drugs in the management of painful neuropathic conditions. Carbamazepine still appears to be the treatment of choice in patients with TGN until more randomized control trials are published with newer anticonvulsants.

Newer anticonvulsants like gabapentin and pregabalin are gaining popularity because of lesser side effects and withdrawal and appears more effective in PDN and PHN.

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